PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 19/00 — A1

(11) International Publication Number: WO 95/29645

(43) International Publication Date: 9 November 1995 (09.11.95)

(21) International Application Number: PCT/US95/05056

(22) International Filing Date: 27 April 1995 (27.04.95)

(30) Priority Data:
08/233,920 28 April 1994 (28.04.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/233,920 (CIP)
Filed on 28 April 1994 (28.04.94)

(71) Applicant *(for all designated States except US)*: HORUS, LTD. [US/US]; Suite 3300, 2001 Sixth Avenue, Seattle, WA 98121-2522 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: HAMDI, Mohamed [CH/CH]; Chemin du Crest-des-Isles 7, CH-1219 Aire (CH).

(74) Agent: GARRISON, David, L.; Suite 3300, 2001 Sixth Avenue, Seattle, WA 98121-2522 (US).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

630-830
830-950

.5-2 J/cm²
10-60 mW

(54) Title: METHODS FOR INHIBITING OR REDUCING MUCOSITIS ASSOCIATED WITH BONE MARROW TRANSPLANT OR PHERIPHERAL STEM CELL INFUSION THERAPIES

(57) Abstract

Prevention or treatment of mucositis in bone marrow transplant patients is achieved by administering laser energy to the affected tissue, the laser light beam being characterized by a wavelength of 630 to 950 nanometers at about 10 to 60 milliwatts and applied to the tissue at the rate of 0.5 to 2.0 joules per cm^2. Periodic treatments before, during and/or after conditioning with agents such as cyclophosphamide and TBI result in reduction of severity of symptoms observed in mucositis.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

Methods for Inhibiting or Reducing Mucositis Associated with Bone Marrow Transplant or Peripheral Stem Cell Infusion Therapies

Technical Field

The present invention relates to the field of tissue degeneration and more particularly to the prevention or reduction of mucositis in mammals undergoing chemo- and/or radiotherapy in conjunction with bone marrow transplant or peripheral stem cell infusion techniques by the application of low level laser energy.

Background Art

It is well established that light has a biological effect on cellular matter. At the membrane level, it is generally believed that photons are converted into electrons via the A^3 cytochrome respiratory cycle. At the ionic level, the absorption of light energy is dictated by the frequency of the light as it encounters various cellular matter. For example, light that is strongly absorbed by molecular water may only be weakly absorbed by certain cellular constituents such as mitochondria. Consequently, the wavelength of light is chosen for its intended purpose.

It has been found that optimal absorption of light energy by cellular and intercellular matter occurs at wavelengths of between about 630 to 830 nanometers in continuous laser light beams, where the power is expressed in milliwatts, and wavelengths of between about 830 to 950 nanometers in pulsed beams,in which the power is usually expressed in watts. Because of the relatively narrow bandwidth of molecular absorption by cells of any particular type, it is desirable to have a light source emitting a substantially uniform wavelength of light. While less flexible as far as choice of wavelengths are concerned, laser light emissions are considered highly desirable because they provide a source of coherent and generally monochromatic light that is ideal for use in

therapeutic applications t the body.

Because of the desirable attribut s f laser light as it relates to bi mechanics, there has been considerable interest in the medical application of laser technology. For example, CO^2 lasers are often used in surgical procedures. Because emissions from these lasers are strongly absorbed by water, this type of laser is usually of the high power type having predominantly thermal effects. At the other end of the spectrum are low level laser devices that produce essentially a thermal light. Those devices emitting light energy between the ranges of about 630 and 950 nanometers do not cause significant tissue damage (excluding damage to photosensitive tissues such as photoreceptors in the eyes) and are thought to result in increased metabolism of tissues, decreased sensitivity to pain, and increased rates of tissue repair.

In the field of cancer treatment, a serious side effect of chemo- radiotherapy is the degeneration of mucosal tissue, or oral mucositis. Oral mucositis is generally characterized by mucosal erythema, atrophy, ulceration, and edema. The frequency and severity of oral mucositis is related to the dose of chemotherapeutic drugs or radiation. Often times the severity of oral mucositis causes the treatment or conditioning regimen to be terminated or severely limited. Consequently, it is of extreme importance to minimize or eliminate the onset of this condition.

Recently, it has been reported that the use of low level laser energy from a HeNe laser has reduced the buccal side effects of fluorouracil chemotherapy. See Pourreau-Schneider, et al., "Soft-Laser Therapy for latrogenic Mucositis in Cancer Patients Receiving High Dose Fluorouracil: A Preliminary Report", J. Natl. Cancer Inst., 84:358-59, 1992. In this retrospective study, it was found that in patients who received low level laser energy treatment (10-1 5 milliwatt) after manifestation of mucositis, the repair time f r grade IV lesions was

reduced by more than half. For patients who received laser therapy prior to and during conditioning th rapy, the incidence of lesions was almost eliminated.

From this initial study concerning oral mucositis, it was not known, however, if such results would be observed in patients undergoing bone marrow transplantations or peripheral stem cell infusion techniques. Currently, methods such as oral rinsing with 0.9% saline solution and routine oral hygiene are only marginally effective in treating oral mucositis occurring as a side effect of chemoradiotherapy widely used in cancer treatments. Other methods rely principally on treating the symptoms of oral mucositis. There is no established preventative treatment for oral mucositis. Thus, it would be desirable to establish the efficacy of photobioactivation as a means to prevent or inhibit the onset of, or decrease the healing time of, mucositis resulting from chemo-radiotherapy when applied in conjunction with bone marrow transplant or peripheral stem cell infusion therapy.

Summary of the Invention

In the aspect discussed herein is a method of a) identifying a candidate for treatment; b) initiating body regimens to the body of the candidate; c) performing the desired procedure on the candidate; d) directing low level coherent energy at periodic intervals to a specific part of the candidate.

In another aspect disclosed herein is a method for directing low level energy at periodic intervals to a living organism.

Disclosure of the Invention

The present invention is characterized as methods to inhibit or significantly reduce mucositis induc d by chemo- or radiotherapy conditioning used in b ne marrow transplant or peripheral stem cell infusi n techniques by controlled use of low level laser energy.

Use of low level laser energy on mucosal cells prior to and/ r during chemo- and/or radiotherapy used in c njunction with bone marrow transplantation or stem cell infusion therapies significantly reduces or eliminates the manifestation of mucositis. In particular, low level laser energy of between 0.5 and 2.0 joules per cm2 operating at a wavelength of between about 630 to 830 nanometers in continuous laser light beams, where the power is expressed in milliwatts, and wavelengths of between about 830 to 950 nanometers in pulsed beams,in which the power is usually expressed in watts which is directed to mucosal tissue was found to be effective in the prevention or mitigation of mucositis resulting from chemo- and/or radiotherapy conditioning associated with bone marrow transplantation or peripheral stem cell infusion techniques. Post conditioning treatments with low level laser energy has been found beneficial when administered for up to twenty one days after conditioning, and may be found to be beneficial beyond that time period.

In a preferred embodiment, a laser having an output wavelength of about 632 to 904 nanometers and an output power of about 10 to 60 milliwatts is directed to mucosal tissue for approximately ten (10) seconds with the tissue energy exposure being preferably 1.5 joules/cm^2. The duration of energy exposure is preferably determined by multiplying the energy output per unit area of the laser by the surface area to be treated, and dividing the product by the power output of the laser for the desired wavelength. Thus, (E joules/cm^2 x S cm^2) x (P watts)$^{-1}$ = Exposure duration (seconds). It can be seen that by altering the output of the laser, the exposure duration will be directly changed. Helium-Neon laser emitting light at 632.8 nanometers is the most preferred laser light source.

To ensure proper exposure of tissue to the laser light, a fiber optic wand may be advantageously used for l calized application of the laser beam to the affected area in a random or set pattern. Another preferred method

includes using a beam scanning application wherein the treated surface is exposed to a controlled beam scan so as to provide a large, uniform area of exposure. Because the energy exposure is a function of time, power, and treated area, a more efficient exposure can be carried out using a programmed scanning of the treatment area. The scanning pattern can be either horizontal, vertical, or generally orbital depending upon the particulars of the treatment area. It is recommended, however, that the scanned area not be too large, e.g. 100 cm^2 so as to introduce exposure variables such as effective laser beam residence time in any particular area within the scanned pattern.

Brief Description of Drawings

Fig. 1 shows a graph of absorption versus wavelength to illustrate the selectivity of certain tissues to specific light wavelengths;

Fig. 2 shows a perspective view of a preferred laser apparatus used in carrying out the invention; and

Fig. 3 shows an enlarged plan view of the control panel shown in Fig. 2.

Best Mode for Carrying Out the Invention

As described previously, the invention concerns the application of a low level laser light to mucosal tissue to reduce or eliminate the negative side effects associated with bone marrow transplantation and/or peripheral stem cell infusion techniques. As is shown in Fig. 1, different tissue types absorb light differently. As shown, the absorption (or transmission) of light energy by the basal layer is different than the absorption of light energy by skin. Consequently, only specific frequency ranges of light are appropriate for use in therapeutic applications. Research conducted by the inventor and others has indicated that laser light in the range between 630 and 950 nm is most effective in stimulating metabolism of cellular respiration and phosphorylation, and collagen synthesis; decreasing

inflammation, and moderating neurotransmission of pain signals.

In a recent study concerning bone marrow transplantation, it was found that by initiating a treatment of oral mucosal tissue with laser stimulation using a Helium Neon laser emitting light at a wavelength of 632.8 nm after the completion of conditioning regimens associated with transplantation, a significantly decreased occurrence of oral mucositis was observed. In this study, each of ten patients were exposed to a 25 milliwatt HeNe laser on either the right or left half of oral mucosa; the contralateral side served as an internal control. The laser treatments were conducted for five consecutive days beginning after transplantation, with each treatment having an exposure level of one joule/cm^2 to the treated areas. After evaluating the patients every three days for 21 days or until discharge, an analysis of the data was performed. The results of the analysis showed that mucosa receiving laser exposure was less painful and that significantly less mucositis occurred .

A subsequent study was conducted to determine if higher levels of exposure were appropriate. In this phase 111 blinded study, 24 autologous bone marrow transplant patients undergoing conditioning with cytophosphamide and TBI were involved. One half of the patients received preventative daily laser applications for twenty one days after conditioning at the dose of 1.5 joules/cm^2 (using a 632.8 nanometer, 60 milliwatt HeNe laser) while the other half constituted the control group and was administered a "placebo" in place of the laser treatment. The laser beam was applied in a continuous emission mode for 10 seconds to 15 points equally distributed inside six selected zones of the oral mucosa. The patients were monitored and evaluated from the transplant day to day 21. After statistically comparing the data, there was a statistically significant decrease in the incidence, the severity, and the duration of conditi ning-induced ral mucositis in bone marrow transplant patients after

preventative use of the laser.

Extending upon this research, a non-blinded study was conducted with 10 patients to determine the efficacy of different wavelength lasers as a preventative or mitigating treatment for oral mucositis. The traditional HeNe laser was used in addition to a Gallium Arsenide (GaAs) laser emitting monochromatic light as a wavelength of 904 nm. All patients received daily laser therapy seven days prior to transplantation. Six sites in the oral cavity were treated and subsequently examined approximately every other day after transplantation. At the conclusion of the study, the results were compared to historical disease/treatment matched control groups. The finding indicated that HeNe laser treated patients had a mean mucositis score of 22.9, the GaAs treated patients had a mean mucositis score of 24.0, and the control group a mean score of 29.1. The treated groups also reported less pain: HeNe 21.8 mm, GaAs 17.7 mm, and control 33.1 mm. There was a trend for the HeNe laser treated patients to have lower mucositis and pain scores on all evaluation days as compared to the control group; the GaAs treated patients did not have lower mucositis scores versus the control group until about days 10-12 whereupon they resolved more quickly. The GaAs treated patients consistently had the lowest pain scores. Interestingly, the HeNe treated patients had lower mucositis scores than the GaAs treated patients until about days 10-12, whereupon the trend reversed. It was also found that the laser therapy was not toxic nor did it create adverse effects.

From the foregoing, it can be seen that treatment of mucosal tissue prior to and during conditioning therapy in conjunction with bone marrow transplantation significantly mitigates or eliminates mucositis and oral pain. Treatment of mucositis with laser light also enhances the resolution f the condition. Because of the similarities of conditioning between bone marrow transplantation and peripheral stem cell infusion,

similar findings are expected.

In rder to carry out the foregoing m thods, an appropriate laser apparatus should be used. Such an apparatus is shown in Fig. 2 and is manufactured by FRADAMA S.A. of Switzerland. This apparatus, or other similar devices were used in the previously described studies. The apparatus comprises a base 1 on rollers, a support column 2, a high voltage power supply 3 and a laser operating unit 4. Control panel 8, shown in enlarged view in Fig. 3, include rotary switches 26-31 to control position, amplitude and frequency in the x and y axes as shown. Pulse repetition rate of 1 or 10 hz can be selected by switches 32 and 33. Keys 34-41 control or display the mentioned function. Displays presenting time 42,frequency 43 and detection sensitivity 44 provide visual information on the performance of the device. A switch for the infrared probe is provided at 46 and the IR control 46, test 47 and frequency multiplier 48 display or control the infrared probe. The He-Ne laser output to scanning or fiber optic probe is controlled at switch 45. Consequently, soft laser applications in various wavelengths can be carried out with a single unit. The fiber optic wand can readily be used to apply laser beam to specific areas for treatment. The scanning mode, on the other hand can be used for general application of laser energy to large areas and a treated area can be exposed to laser light without the necessity of the operator aiming or "waving" the applicator wand over the area to be treated. Moreover, by knowing the scanning area, the operator can more accurately maintain consistent exposure levels of laser light to treated area. A more detailed discussion of the apparatus is available from the manufacturer in its S601 R Instruction manual which is hereby incorporated by reference.

CLAIMS

1. A method for treating or preventing oral mucositis in mammals involved in procedures for bone marrow transplantations or peripheral stem cell infusions and/or for mitigating oral pain associated with procedures for bone marrow transplantations or peripheral stem cell infusions, said method comprising the steps of:

(a) identifying a candidate for bone marrow transplant or peripheral stem cell infusion;

(b) initiating conditioning regimens for bone marrow transplant or stem cell infusion which includes chemo- and/or radiotherapy;

(c) performing a bone marrow transplant or peripheral stem cell infusion; and

(d) directing low level laser energy to mucosal tissue at periodic intervals over a period of time.

2. A medical device for treating or preventing oral mucositis in mammals involved in procedures for bone marrow transplantations or peripheral stem cell infusions and/or for mitigating oral pain associated with procedures for bone marrow transplantations or peripheral stem cell infusions, said device having means to direct coherent energy at an object at periodic or constant times, use of said device comprising the steps of:

(a) identifying a candidate for bone marrow transplant or peripheral stem cell infusion;

(b) initiating conditioning regimens for bone marrow transplant or stem cell infusion which includes chemo- and/or radiotherapy;

(c) performing a bone marrow transplant or peripheral stem cell infusion; and

(d) directing low level laser energy from said device to mucosal tissue at p riodic intervals over a period of time.

3. Use of a low level coherent energy device for treatment or prevention of oral mucositis in mammals involved in procedures for bone marrow transplantations or peripheral stem cell infusions and/or for mitigation of oral pain associated with procedures for bone marrow transplantations or peripheral stem cell infusions, said use comprising the steps of:

(a) identifying a candidate for bone marrow transplant or peripheral stem cell infusion;

(b) initiating conditioning regimens for bone marrow transplant or stem cell infusion which includes chemo- and/or radiotherapy;

(c) performing a bone marrow transplant or peripheral stem cell infusion; and

(d) directing low level laser energy from said device to mucosal tissue at periodic intervals over a period of time.

4. The method, device or use of claim 1, 2 or 3 wherein step (d) is commenced prior to step (b).

5. The method, device, or use of claim 1, 2, or 3 wherein the mucosal tissue is oral tissue.

6. The method, device, or use of claim 1, 2, or 3 wherein the low energy laser therapy is conducted with laser light having a wavelength of one of:

between about 630 and 950 nanometers;

about 632 nanometers;

about 830 nanometers;

about 904 nanometers.

7. The method, device, or use of claim 1, 2, or 3 wherein the output power of the laser used is between 10 milliwatts and 60 milliwatts.

8. The method, device, or use of claim 1, 2, or 3 wherein the dose of low level laser light is between 0.5

and 2.0 J ules/cm^2

9. The method, device, or use of claim 1, 2, or 3 wherein step (d) is continued for about one to fourteen days subsequent to the termination of conditioning therapy or wherein step (d) is continued for about one to twenty one days subsequent to the termination of conditioning therapy.

10. The method, device or use of claim 1, 2 or 3 wherein the application of low level laser energy is by machine controlled scanning or a fiber optic transmission system.

11. A method for directing low level energy at periodic intervals on a living organism.

12. Use of a low level energy device for treating or preventing oral mucositis and/or for mitigating pain, said device being directed at the effected area and caused to emanate low level energy at periodic intervals over a period of time.

13. A medical device for treating or preventing oral mucositis and/or for mitigating pain, said device being comprised of means for emanating low level coherent energy in periodic increments.

14. A method of using a low level coherent energy device in periodic bursts to treat a living organism, said method comprising:

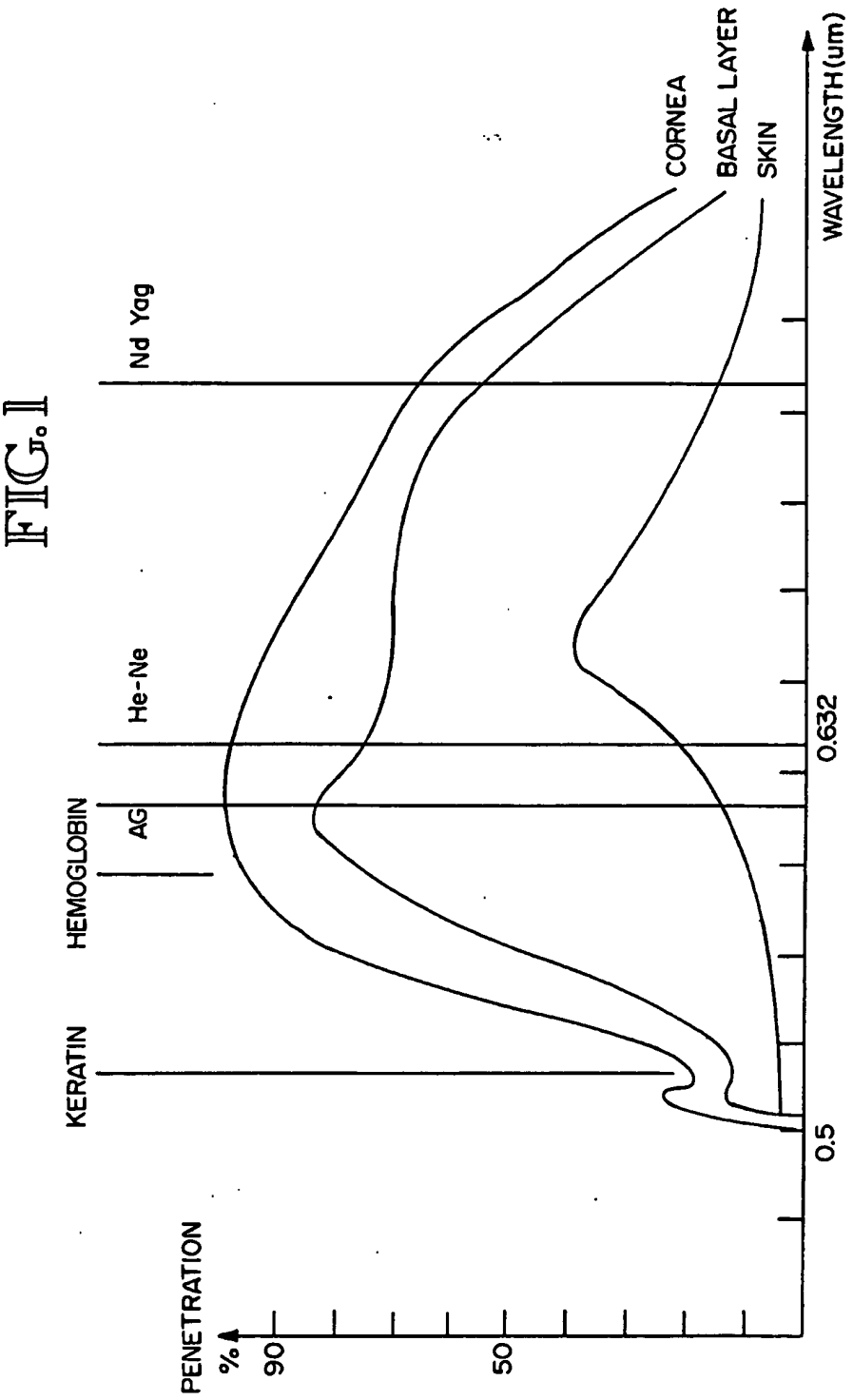
identifying an organism for treatment;

initiating conditioning regimens to the body of the organism;

performing a desired procedure on the organism;

directing low level coherent energy at periodic intervals.

FIG. 1


PENETRATION
%
90
50
KERATIN
HEMOGLOBIN
AG
He-Ne
Nd Yag
CORNEA
BASAL LAYER
SKIN
0.5
0.632
WAVELENGTH(um)

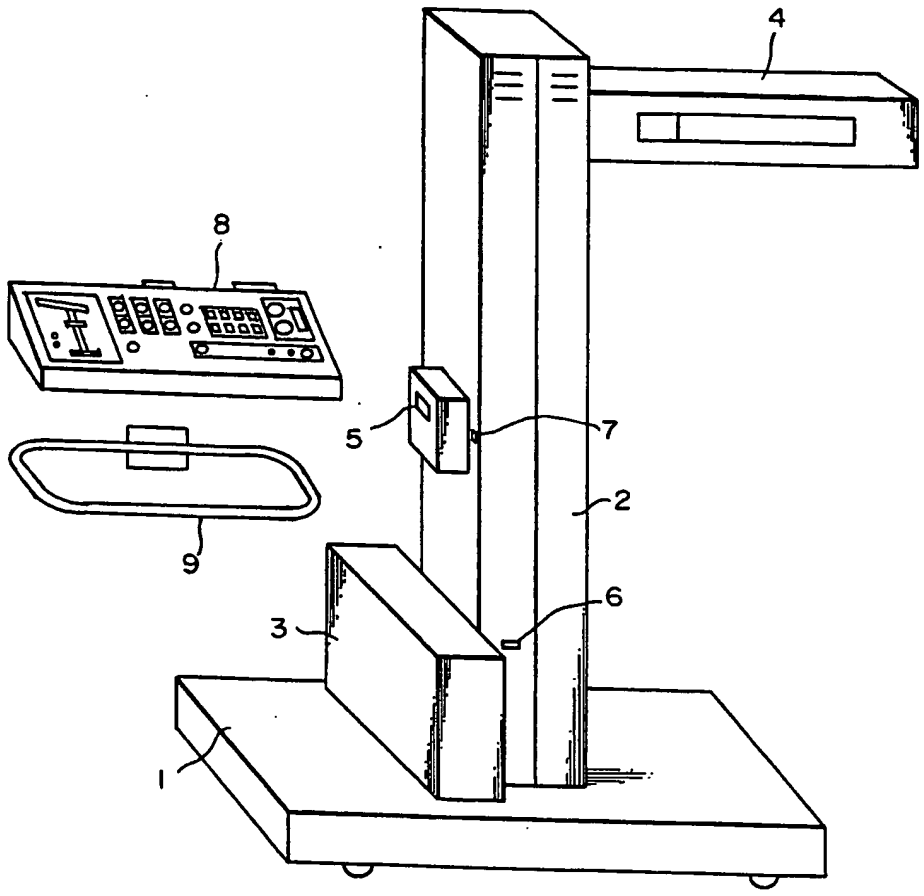


FIG. 2

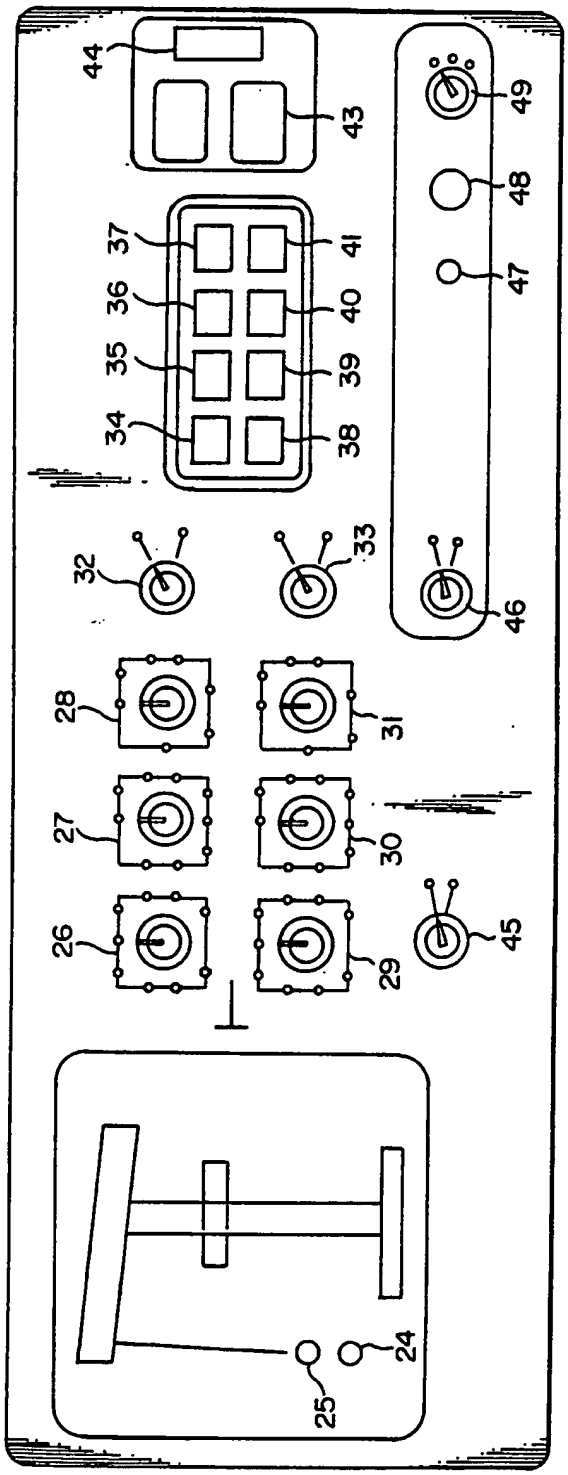

44
43
49
48
47
37
41
36
40
35
39
34
38
32
33
46
28
31
27
30
26
29
45
24
25

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/05056

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 19/00
US CL :128/898

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/897, 898; 607/089

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Journal of the National Cancer Institute, Vol.84, No. 5, March 4, 1992, pp.358 and 359, CORRESPONDENCE. (NATALIE POURREAU-SCHNEIDER ET AL.), Soft-Laser Therapy for Iatrogenic Mucositis in Cancer Patients Receiving High-Dose Fluorouracil: A Preliminary Report.	11-14 ---------- 1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 31 MAY 1995	Date of mailing of the international search report 16 JUN 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOHN P. LACYK Telephone No. (703) 308-2995

Form PCT/ISA/210 (second sheet)(July 1992)*